

Review

A New Approach to Managing Oral Manifestations of Sjogren's Syndrome and Skin Manifestations of Lupus

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Sjögren's syndrome (SS) is an autoimmune disorder that affects the salivary glands, leading to xerostomia, and the lacrimal glands, resulting in xerophthalmia. Secondary SS is associated with other autoimmune disorders such as systemic rheumatic diseases and systemic lupus erythematosus (SLE), which can affect multiple organs, including the epidermis. Recent studies have demonstrated that green tea polyphenols (GTPs) possess both anti-inflammatory and anti-apoptotic properties in normal human cells. Epidemiological evidence has indicated that, in comparison to the United States, the incidence of SS, clinical xerostomia and lupus is considerably lower in China and Japan, the two leading green tea-consuming countries. Thus, GTPs might be responsible, in part, for geographical differences in the incidence of xerostomia by reducing the initiation or severity of SS and lupus. Consistent with this, molecular, cellular and animal studies indicate that GTPs could provide protective effects against autoimmune reactions in salivary glands and skin. Therefore, salivary tissues and epidermal keratinocytes could be primary targets for novel therapies using GTPs. This review article evaluates the currently available research data on GTPs, focusing on their potential application in the treatment of the oral manifestations of SS and skin manifestations of SLE.

Keywords: Catechins, Green tea, Lupus, Sjogren's syndrome, Xerostomia

Introduction

Clinical background and epidemiology. Sjogren's syndrome (SS) is an autoimmune disorder that affects multiple exocrine

glands, particular those that produce moisture to coat exposed epithelia such as the oral and ocular surfaces. Primary Sjogren's syndrome (pSS) is associated with lymphocytic infiltration of the salivary and lacrimal glands and eventual atrophy of these tissues, leading to a loss of fluid production. The salivary component of pSS is defined as xerostomia, with symptoms generally referred to as salivary hypofunction (Daniels and Fox, 1992). Salivary functions are crucial to human oral health. Saliva provides lubrication, buffering capacity, protection of the mineral surfaces of the teeth, and antibacterial activities. It also provides a route of excretion (e.g., for lead, mercury, and thiocyanate), and a possible endocrine function (antigonadotrophins). The parotid gland is involved in iodide metabolism, and possibly participates in thyroxin metabolism (Banerjee and Datta, 1986, Geiszt *et al.*, 2003). A variety of salivary components, including an array of specialized proteins synthesized by the glands, mediate these functions. Salivary proteins include mucins (lubrication), lysozyme (antibacterial), proline-rich proteins (participate in formation of the enamel pellicle and in enamel surface mineralization), statherin (helps maintain saliva supersaturated in calcium & phosphate to drive enamel remineralization, and may inhibit calculus formation), and histatins (antifungal peptides). It also contains blood clotting factors and growth factors (NGF, EGF and others). Tears provide many of the same functions to the eye, and the lacrimal glands produce a related set of proteins. Thus, in addition to the decrease in the volume of the glandular secretions in SS, reduction in the ability to produce these proteins compromises the functionality of the secretions.

Diagnosis of SS is currently based on various established criteria used throughout the world (Vescovi *et al.*, 2004). The diversity and complexity of symptoms in this multi-tissue disorder increase the difficulty of accurate diagnosis and effective treatment (Kassan and Moutsopoulos, 2004). If not treated properly, xerostomia may lead to oral complications (Daniels and Wu, 2000) that include difficulty in speech and chewing, decline in taste sensation, increased oral bacterial counts, caries and gingival recession, fissuring, and ulceration

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of the mucosa and angles of the mouth. Patients with xerostomia are evaluated for various treatments, including 1) ongoing dental decay prevention and treatment supervised by their dentist; 2) salivary flow stimulation; 3) recognition and treatment of chronic oral candidiasis; 4) selective use of saliva substitutes; and 5) a review of xerostomic prescription drugs (Daniels, 2000). Many of the same issues concern the eye in SS.

SS affects 1-4 million people in the United States, and 90% of patients are females. The peak incidence of onset is between the ages of 40 and 60. SS results in a significant decrease in the quality of life for patients. Importantly, SS is considered under-diagnosed, under-treated and under-researched (Venables, 2004). Therefore, SS has considerable significance from a public health perspective.

Estimates of the prevalence of SS are affected by the criteria used for diagnosis. However, genuine differences between various regions and communities exist (Fox, 1997, Vitali *et al.*, 2002). The world-wide distribution is believed to be 1/2500 (Kang *et al.*, 1993). In the United States, SS affects approximately 1% of the population (Carsons, 2001). In China, one regional study with 26,000 subjects suggested the prevalence of primary SS was only 0.03% (Zhang, 1995). In Japan, the estimated crude prevalence rates for SS were only 0.001 in males and 0.026 in females (Yoshida, 1999). A survey conducted by the Japanese Ministry of Health and Welfare indicated the SS prevalence was just 0.06% among females (Miyasaka, 1995). As for xerostomia, one study showed that among a group of 1003 Japanese individuals with an average age of 66, about 9.1% experienced dry mouth during eating (Ikebe *et al.*, 2001), whereas in the United States, one epidemiological study found that in a group of 2481 individuals aged 65-84 years old, 27% reported either dry mouth or dry eyes (Schein *et al.*, 1999), and another found that dry mouth ranged from 10% among persons over age 50 to 40% for persons over age 65 (Billings *et al.*, 1996). Although there is a lack of direct statistical comparison between the U.S. population and either the Japanese or Chinese population, it is apparent that SS and xerostomia are more prevalent in the U.S. population, particularly amongst the elderly.

When SS occurs absent other autoimmune disorders it is called primary SS (pSS). Secondary SS refers to SS that develops in association with an existing autoimmune disease, such as systemic lupus erythematosus (SLE) (Rehman, 2003, Mahoney and Spiegel, 2003). Lupus is a complex disease, and clinical classification of lupus includes systemic lupus erythematosus (SLE), drug-induced lupus, neonatal lupus, lupus profundus (J Rheumatol. 1999 Jan; 26(1): 68-72), discoid lupus erythematosus (DLE), and subacute cutaneous lupus (SCLE). SLE is the most prevalent form, characterized by recurrent, widespread and diverse organ involvement. It may affect multiple organs and tissues such as joints, skin, kidneys, heart, lungs, blood vessels, and the brain (National Institute of Arthritis and Musculoskeletal and Skin Diseases).

Lupus can cause extreme exhaustion, fevers, skin rashes, and can lead to scars, renal failure, central nervous system lesions and death (US HHS Office of Minority Health Resource Center [OMHRC], 2001). Approximately one third of deaths occur among men and women younger than 45. During 1979-1998, the annual number of deaths from lupus rose from 879 to 1,406 and the crude death rate increased from 39 to 52 per million population, with a total of 22,861 deaths reported during this 20-year period (US CDC Office of Communication, 2002).

Due to the lack of definitive epidemiological information on lupus, the exact number of people with this disease is unknown. Based on existing data, researchers believe at least five million people worldwide have lupus and more than 100,000 new cases develop every year, though it is likely that these estimates are low (Lupus Foundation of America, 2001). Lupus affects up to 0.4% of the population in the United States, mostly young females of childbearing age, with an approximately 9:1 ratio between females and males (US National Women's Health Information Center [NWHIC], 2003). In China, regional studies demonstrated that 0.03%-0.07% of the population is affected by lupus (Huang, Zhang and Shi, 1985). This number is considerably lower than that of the U.S. population.

The skin is one of the most commonly affected tissues in lupus. It is believed that cutaneous manifestations of LE affects 14.6 to 68 per 100,000 people (Callen, 2004). About 75% of people with SLE will subsequently develop some type of skin problem. Conversely, about 50% of SLE patients have skin lesions as their initial symptom. Besides skin problems seen in other diseases, there are three types of skin lesions unique to lupus: chronic cutaneous LE (CCLE); subacute cutaneous LE (SCLE); and acute cutaneous LE (ACLE). Discoid LE (DLE) is the most common form of CCLE. Among the estimated 1.5 million U.S. patients suffering from lupus, 10% are DLE patients (Lupus Foundation of America, 2005). DLE is characterized by coin-shaped, red, scaly, thickened lesions, commonly on the scalp and face. These lesions can scar. Some lupus patients initially have only DLE lesions. About 10% of these people progress to SLE. SCLE has two clinical forms: papulosquamous SCLE is characterized by erythematous elevated areas of scaly skin that can resemble psoriasis; the other form consists of red, annular lesions. Both forms are very photosensitive, and occur on the sun-exposed areas of the arms, shoulders, neck and trunk. Approximately 50% of patients with SCLE will also have SLE. Localized ACLE manifests as a characteristic red, flat, painless so-called butterfly rash over the bridge of the nose (Chaudhry *et al.*, 2005). Generalized ACLE can affect the arms, legs and body. These lesions tend to be very photosensitive, but usually do not produce scarring.

Biomarkers of SS and lupus. There are molecular markers that can be used in addition to histology to monitor SS progression and the effects of agents on the disease. Anti-

nuclear antibodies (ANAs), a group of antibodies that target normal components of a cell nucleus, are found in about 70% of Sjögren's patients. The autoantibodies against major autoantigens SS-A/Ro and SS-B/La are found in about 95% and 87% of primary SS patients, respectively (Rehman, 2003). Elevated mRNA levels of SS-A/Ro and SS-B/La are found in salivary tissues from SS patients. The ubiquitously expressed endogenous autoantigens also include golgin family members, fodrins, nuclear mitotic apparatus protein (NuMA), poly(ADP)ribose polymerase (PARP), Ku, nucleolar organizer region protein (NOR-90), p80 coilin and centromere protein-C (CENP-C) (Rosen and Casciola-Rosen, 2004). Sera from lupus patients also often have high titers of anti-nuclear autoantibodies (ANAs). These autoantibodies specifically target the following autoantigens: dsDNA, Smith antigen (Sm), Sjogren's syndrome (SS)-A/Ro, SS-B/La, poly(ADP)ribose polymerase (PARP), uridine rich 1 small nuclear ribonucleoprotein (U1 snRNP), and ribosomal-P (Reeves, 2004). Lupus-associated autoantigens also include golgins present in the Golgi apparatus and coilin proteins (Nozawa *et al.*, 2002; Stinton *et al.*, 2004). Thus, there is some overlap between the autoantigens targeted in SS and lupus.

Pathogenesis of SS and lupus. The pathogenesis of SS and of lupus, by which affected cells and tissues become targets of the immune system, is poorly understood. The onset of lupus involves 1) genetic alteration leading to tolerance breakdown; 2) exposure of normally hidden nuclear proteins as autoantigens; 3) hypersensitivity of antigen-presenting cells (APCs) that are triggered by infection or ROS-induced DNA repair; 4) subsequent cellular and humeral immune reactions; and 5) further stimulation and amplification of autoimmunity by either intrinsic (complement, immune complexes, cytokines and chemokines) or extrinsic factors, such as infections and ultra violet (UV)-induced apoptosis (Mamula *et al.*, 1994, Ventura *et al.*, 1999; Risch, 2000; Reeves, 2004; Bredberg *et al.*, 2005).

Caspase-mediated apoptosis is believed to be essential to the initiation of autoimmune responses, and apoptosis of epidermal keratinocytes is seen in LE skin lesions (Kuhn *et al.*, 2006). One mechanism by which the autoimmune response may be triggered involves translocation of nuclear autoantigens during an "aberrant" apoptosis onto the cell surface, where they are exposed to APCs such as macrophages and dendritic cells (Cravens and Lipsky, 2002; Manganelli and Fietta, 2003). During keratinocyte apoptosis, autoantigens assemble into distinctive apoptotic bodies and blebs. The smaller blebs contain fragmented endoplasmic reticulum (ER) and ribosomes, as well as SS-A/Ro. The larger apoptotic bodies contain nucleosomal DNA, SS-A/Ro, SS-B/La, and the small nuclear ribonucleoproteins (Casciola-Rosen *et al.*, 1994). Structural changes in certain autoantigens may contribute to an altered immunogenic configuration of the autoantigen cluster (Rosen and Casciola-Rosen, 2004). APCs can cleave the autoantigens and trigger the activation of T cells by presenting

fragments with the assistance of major histocompatibility complex (MHC). Subsequent to T cell activation, an amplified immune response occurs with phagocyte activation, cytolysis, and antibody production in B cells against autoantigens. This results in destruction of target cells or tissues (Reeves, 2004). Thus, aberrant assembly or protein configuration or presentation by APCs, could trigger initiation of the primary immune response to these molecules (Casciola-Rosen *et al.*, 1994, Tan, 1994, Albert *et al.*, 1998).

The skin lesions of patients with lupus are marked by lymphocytic infiltration and elevation of inflammatory cytokines (Amoura *et al.*, 2003). Plasmacytoid dendritic cells (P-DCs) accumulate in the skin of lupus patients, locally producing large amount of IFN α/β (Farkas *et al.*, 2001). IFN α/β enhances the T helper cell-mediated immune response and further induces a spectrum of cytokines (Klimpel *et al.*, 1990; Clark-Lewis *et al.*, 2003; Wenzel *et al.*, 2004). One of these cytokines, tumor necrosis factor- α (TNF α), is believed to play an essential role in both inflammation and apoptosis of epidermal keratinocytes (Aringer and Smolen, 2004).

Ultraviolet light (UV) promotes apoptosis of epidermal keratinocytes (which are then referred to as "sunburn cells." (Daniels, 1961)), and photosensitivity is common in patients with cutaneous LE (Millard *et al.*, 2000). The increased number of apoptotic keratinocytes resulting from UV light exposure subsequently leads to an increased amount of autoantigens (Werth *et al.*, 2004). UV-B at intermediate or high doses is particularly associated with keratinocyte apoptosis/necrosis and release of autoantigens (Caricchio *et al.*, 2003). UVB-induced TNF α was found to elevate SS-A autoantigen expression (Gerl *et al.*, 2005). Previous studies showed that UV induced translocation of autoantigens (SS-A and SS-B) to the surface of either normal or LE-derived keratinocytes, resulting in increased autoantibody production (Furukawa *et al.*, 1990; Golan *et al.*, 1992; Angotti, 2004). Caspases cleave intracellular proteins into fragments that are recognized by autoantibodies from patients with lupus (Casciola-Rosen *et al.*, 1995; Utz and Anderson, 2000). It was suggested that the interaction between antibodies (particularly anti-SS-A/Ro) and UVB-irradiated keratinocytes may induce, through a cytotoxic mechanism, skin lesions in lupus (Norris, 1993, Furukawa *et al.*, 1999).

Reactive oxygen species (ROS) cause oxidative stress that also can trigger DNA breaks and subsequent events, including apoptosis. In addition, ROS may have a role in exposing cryptic epitopes (hidden regions of an antigen) leading to autoantibody production (Cha *et al.*, 2002; Bredberg *et al.*, 2005).

The role of apoptosis in loss of glandular tissue in SS is less clear (Wang *et al.*, 2006). Environmental and genetic factors appear to contribute to the etiology of SS, although the evidence is relatively premature (Bolstad and Jonsson, 2002; Yamamoto, 2003). T-cell-mediated cytotoxicity (Rehman, 2003; Manganelli and Fietta, 2003; Hayashi *et al.*, 2004) and autoantibodies are important in loss of gland function. There

is also a failure to remove autoimmune T-cells at the level of thymic selection, resistance of T-cells within the gland to undergo apoptosis, aberrant expression of increased levels of cell adhesion molecules on glandular epithelial cells (facilitating infiltration of autoimmune lymphocytes to glands), up regulation of human leukocyte antigen (HLA)-DR, and polyclonal activation of B-lymphocytes (Rehman, 2003). Glandular epithelial cells contribute to the autoimmune process by secreting pro-inflammatory cytokines.

Both lymphocyte-mediated cytotoxicity and UV-induced apoptosis involve $\text{TNF}\alpha$, Fas/FasL, proapoptotic Bcl family members (BAX), and caspases, leading to cell death and the translocation of autoantigens (Wang *et al.*, 1999; Bollain-y-Goytia *et al.*, 2000; Zhang *et al.*, 2001). The imbalance of Bcl-2/Bax also plays an important role in the abnormal activity of apoptosis in the glandular cells (Manganelli and Fietta, 2003). UV-induced apoptosis also involves reactive oxygen species (ROS) (Pablos *et al.*, 1999; Lawley *et al.*, 2000). $\text{TNF}\alpha$, interferon- γ (IFN γ) and ROS can activate the p53 pathway, which could lead to growth arrest and apoptosis. Lesional skin from patients with LE exhibited increased numbers of apoptotic cells with elevated p53 expression (Angotti, 2004, Werth *et al.*, 2004).

Current treatment of SS and lupus. At present, there is no known cure for SS, nor is there a specific treatment to restore gland function. Treatment is generally symptomatic and supportive (National Institute of Arthritis and Musculoskeletal and Skin Diseases). For pSS, xerostomia and xerophthalmia,

artificial lubricants are commonly used as saliva or tear substitutes (Baudouin *et al.*, 2004). In recent years, salivary stimulants, such as pilocarpine and cevimeline, have been approved by the FDA to treat xerostomia (Fox, 2003, Cassolato and Turnbull, 2003, Porter *et al.*, 2004). In addition, oral administration of interferon γ (IFN- γ) was effective in improving saliva production in patients with pSS (Khurshudian, 2003). However, long-term adverse effects have not been evaluated for these therapies. It was suggested that gene therapy might be one of the future treatments for pSS by inducing the growth and differentiation of glands (Fox, 2004). On another front, herbal extracts and Chinese traditional medicine have been used to treat SS and/or xerostomia with certain degree of success (Zhao *et al.*, 1989; Ohno *et al.*, 1990). These naturally occurring materials may provide an alternative approach for SS-associated disorders. One group of potentially promising agents is green tea polyphenols.

The treatment plan for lupus depends on the severity of the disease. Several classes of medications are currently prescribed for lupus patients (see Table 1, also Reeves, 2004). These medications mainly target the symptoms by inhibiting inflammation, suppressing the immune system and relieving rheumatoid pain. However, severe adverse effects may occur. Only patients with severe disease affecting internal organs or symptomatic disease refractory to milder options should be exposed to the potential toxicity of long-term corticosteroids and immunosuppressants (Reeves, 2004).

In China, immune-mediated disorders have been treated by Chinese herbal extracts for centuries. Studies using certain

Table 1. Pharmacological therapies for lupus and related conditions currently available

Class	Examples	Uses
	Generic name	
Non-steroidal anti-inflammatory drugs	Ibuprofen	Relief of inflammatory pains in muscles, joints, serosae etc.
	Naproxen	
	Indomethacin (previously used)	COX-2 inhibitors (for high risk gastrointestinal bleeding patients)
	Celecoxib	
	Rofecoxib	
Antimalarials	Hydroxychloroquine	Autoimmune-related fatigue, arthropathy and rash; limited evidence of efficacy for sicca, thrombophilia and pain
Corticosteroids	Prednisone, prednisolone	Serositis, cytopenias, major organ involvement; low-dose transient use for refractory musculoskeletal features; high dose taper or low-dose transient use for refractory musculoskeletal features
Immuno-suppressants	Azathioprine Methotrexate (mainly for RA) Cyclosporine Cyclophosphamide Leflunomide Mycophenolate	All immunomodulators used for severe organ involvement or cytopenia, steroid-sparing role where disease relapses with attempted steroid weaning; introduced relatively early in moderate/severe rheumatoid arthritis, renal symptoms and CNS (central nervous system)
Biologicals (anti-tumor necrosis factor antibody, anti-T cell antibody, etc.)	Etanercept	Steroid sparing agents, generally combined with an immunosuppressant agent to reduce signs and symptoms of lupus, especially arthritis

herbal extracts to treat SLE and rheumatoid arthritis have shown inhibitory effects on inflammatory cytokine production and cyclo-oxygenase-2 (COX-2)-mediated prostaglandin E2 production. Plant-derived remedies for treating lupus have also been tested in the mouse MRL/lpr model for autoimmune disease. Oral administration of a Japanese-Chinese traditional medicine, Sairei-to, reduced the amount of IgG deposition at the dermal-epidermal junction, the autoantibody and rheumatoid factor titer, and lymphoproliferation (Kanauchi *et al.*, 1994). However, issues of possible toxicity with these extracts have not been addressed (Ramgolam, 2000). As of today, natural compounds clearly identified as non-toxic have not been used for the prevention of or intervention in autoimmune disorders such as lupus. The latest findings from green tea research, including our finding that the major green tea polyphenol potently inhibits the expression of major autoantigens in human primary epidermal keratinocytes and salivary gland cells, may provide a new approach to treating autoimmune disorders. These findings are reviewed in the next section.

Green Tea as a Potential Weapon against Autoimmune Diseases

Green tea and green tea polyphenols. The tea plant (*Camellia sinensis*) has been cultivated in Asia for thousands of years. Currently, more than two thirds of the world population consumes this popular beverage. However, the majority of the tea consumed in the world is black tea (78%), produced through complete oxidation (fermentation). Green tea, which is processed with minimal oxidation, comprises only 20% of world-wide consumption (Kuroda and Hara, 1999). Green tea polyphenols (GTPs), also more specifically referred as green tea catechins, are a group of polyphenolic compounds present in the leaves of *Camellia sinensis*. These are converted into polymeric black tea polyphenols during the fermentation process that produces black tea. The major green tea polyphenols are (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epigallocatechin-3-gallate (EGCG). EGCG is the most abundant and widely studied green tea polyphenol (Mukhtar and Ahmad, 2000; Katiyar and Elmets, 2001; Yang, 2002). Research during the past 20 years has demonstrated that GTPs are potent antioxidants that also possess chemopreventive, anti-apoptotic, and anti-inflammatory activities. These properties of GTPs are consistent with their apparent beneficial effects against a range of diseases (Mukhtar and Ahmad, 2000; Green tea, 2000; Sueoka *et al.*, 2001). An epidemiological study with 8552 subjects indicated that the life span of both females and males was positively correlated with the amount of green tea consumed. Among these subjects, cancer, cardiovascular diseases and diabetes mellitus were inversely correlated with the amount of green tea consumption (Imai and Nakachi, 1995; Imai *et al.*, 1997; Sueoka *et al.*, 2001). Conversely,

these studies suggest that there are few, if any, adverse consequences from consumption of green tea. Consumption of green tea is high in China and Japan, regions where the incidence of SS, lupus and xerostomia are substantially lower than the U.S.

Anti-inflammatory effects. Evidence collected from an epidemiological study of 31336 females ages 55-69 years, conducted from 1986 to 1997, concluded that there is an inverse association between tea consumption and the onset of rheumatoid arthritis (RA). The relative risk (RR) of RA decreased to 0.39 in women consuming >3 cups of tea (unspecified) per day compared to women who never consumed tea (Mikuls *et al.*, 2002). Recent investigation of the anti-inflammatory effects of green tea has shown promising results (Curtis *et al.*, 2004). Studies using transgenic mice demonstrated that both TNF- α and IL-6 (cytokines associated with inflammation) were inhibited at the transcriptional level by 0.1% green tea extract in the feeding water, which suggests that green tea may be useful to prevent or ameliorate diseases associated with cytokine overexpression (Sueoka *et al.*, 2001). The inflammatory cytokine IL-1 increases the production and activity of matrix metalloproteinases (MMPs). It was found that EGCG effectively inhibited IL-1 β -induction of MMP-1 and MMP-13 (Ahmed *et al.*, 2004), and the inhibition of IL-1 β signaling may occur through the modulation of the mitogen-activated protein kinase (MAPK) pathway components (Singh *et al.*, 2003). EGCG also showed inhibitory effects on IL-1 β -mediated inflammatory pathways (Wheeler *et al.*, 2004). A recent study showed that EGCG suppressed LDP-induced dendritic cell (DC) maturation, therefore reducing the subsequent T cell activation (Ahn *et al.*, 2004).

Antioxidant and anti-apoptotic effects. GTPs rapidly scavenge ROS, providing a line of defense *in vivo*, and they also inhibit "pro-oxidant" enzymes, such as nitric oxide synthase, lipoxygenases, cyclo-oxygenase (COX), and xanthine oxidase (Frei and Higdon, 2003). Green tea consumption by humans leads to an increase of secreted salivary GTPs, in a concentration range 10 times higher than the serum levels (<10 μ M) (Yang *et al.*, 1999). EGCG in the 15-100 μ M range, physiologically achievable via oral consumption (Yang *et al.*, 1999), suppressed ROS in immortalized human salivary gland acinar cells (NS-SV-AC, Azuma *et al.*, 1993) in a dose-independent manner (Yamamoto *et al.*, 2003).

GTPs provide a "shield effect" against UVB-induced oxidative stress. Both *in vivo* and *in vitro* studies have demonstrated that GTPs provide strong protection to epidermal keratinocytes against UVB-induced apoptosis. Topical application of GTPs caused a dose-dependent inhibition of the erythema response induced by UV radiation; it reduced the number of burnt cells and the amount of DNA damage (Elmets *et al.*, 2001). Topical application of GTPs (5 mg/animal) or EGCG (1 mg/cm² of skin) prior to UVB exposure in SKH-1 hairless mice significantly

prevented UVB-induced depletion of the antioxidant enzymes, inhibited UVB-induced oxidation, and inhibited UVB activation of MAPK family members (Vayalil *et al.*, 2003, Afaq *et al.*, 2003). Consistent with these effects, we previously reported that EGCG protected human salivary acinar and duct-derived cells from radiation and chemotherapeutic drug-induced apoptosis (Yamamoto *et al.*, 2004).

GTPs potently inhibit production of TNF- α , a pro-apoptotic cytokine (Yang *et al.*, 1998). EGCG inhibits TNF- α -mediated activation of the nuclear factor- κ B (NF- κ B) pathway; thereby protecting normal cells from TNF- α -induced apoptosis (Wheeler *et al.*, 2004). Collectively, these studies demonstrate that GTPs have a range of beneficial activities. They can inhibit apoptosis, a mechanism implicated in SS and lupus, and they suggest that modulation of signaling via MAPK pathways may be a mechanism of action. However, the relative contributions of the antioxidant and signal pathway modifying properties of GTPs to protection from a given stress have not been fully elucidated.

Anti-autoimmune disease effects of GTPs. As noted above, there is an inverse association between tea consumption and the onset of rheumatoid arthritis (RA). In a mouse model for rheumatoid arthritis, oral administration of 0.2% of GTPs significantly reduced the protein levels of COX-2, IFN- γ , TNF- α and IgG in the joints, and resulted in a more than 50% reduction of collagen-induced arthritis (Haqqi *et al.*, 1999). Similarly, in a mouse model for autoimmune encephalomyelitis, oral administration of EGCG reduced clinical severity when the compound was given at initiation or after the onset of symptoms both by limiting brain inflammation and by reducing neuronal damage; these effects were accompanied by abrogated proliferation and TNF- α production in encephalitogenic T cells (Aktas *et al.*, 2004). Both *in vitro* and *in vivo* studies demonstrated that EGCG effectively protected animals from MLD-STZ-induced diabetes (a model for type I diabetes) by protecting pancreatic islets, suggesting a possible therapeutic value of EGCG for the prevention of diabetes mellitus (Yang *et al.*, 1998). In a lupus erythematosus (LE) mouse model MRL/MpJ-*Fas*^{lprcg}/*Fas*^{lprcg} (MRL-*lpr*^{cg}), mice were fed with 2% green tea powder diet for 3 months. The green tea-fed group showed a prolonged survival period with reduced lymph node hyperplasia and reduced levels of anti-DNA antibodies (Sayama *et al.*, 2003). Taken together, these data show that GTPs can reduce the severity of autoimmune diseases in animal models, and that one mechanism could be reduction of inflammatory cytokine production, possibly through modulation of the MAPK pathway.

Recently discovered protective effects of EGCG against autoimmune disorders. In our study aimed at identifying green tea-targeted human genes using the Affimetrix gene array system, we recently discovered that EGCG at attained topical or orally administration levels (50-100 μ M), modulated approximately 2100 human genes by 2-fold or more. Most

interestingly, EGCG inhibited the expression of many autoantigen genes. To verify the gene expression results, subsequent RT-PCR and Western blot analyses were performed using normal human epidermal keratinocytes (NHEK) and immortalized normal human salivary gland acinar cells (NS-SV-AC). Data from these experiments demonstrated that EGCG exposure resulted in a significant reduction of autoantigens, including SS-A, SS-B, fodrin, centromere protein C, golgin-67, coilin, and PARP (Hsu *et al.*, 2005). Data from our animal studies suggest that GTPs reduced the magnitude of salivary lymphocyte infiltration and decreased serum total autoantibody levels in an accepted mouse model of SS, the NOD mouse, and a model of LE, MRL mice (Hsu *et al.*, 2006).

The NOD mouse is an important model system that has provided clues to the cellular mechanisms involved in SS (Cha *et al.*, 2002). This mouse strain develops a lymphocytic infiltration of exocrine tissues at 10-12 weeks of age, particularly in females, and was originally used as a model for type I diabetes. NOD-*scid* congenic mice (that lack functional lymphocytes) do not develop sialadenitis (or diabetes). However, they do show dysfunction in expression of biochemical markers of salivary gland differentiation such as amylase and parotid secretory protein (PSP). These facts are consistent with a model for SS in which there is an initial phase during which dysregulation of glandular homeostasis triggers the disease, followed by an immune cell-mediated phase that leads to a loss of secretory function (Cha *et al.*, 2002). Collectively, observations on the protective role of GTPs against the damage incurred by autoimmune disorders suggest that three potential major strategies for ameliorating SS directly involving the acinar cells could be selective inhibition of i) their apoptosis, ii) autoantigen expression, and iii) production of pro-inflammatory cytokines.

Mitogen-activated protein kinase (MAPK) pathways are involved in signal transduction in salivary gland cells. The multiple MAPK signal transduction pathways are involved in the control of diverse cellular events including proliferation, differentiation and apoptosis. Gene expression in salivary epithelial cells is regulated, in part, *via* the Raf/MEK/MAPK pathway (Slomiany and Slomiany 2002a, Li *et al.*, 1997). It was found that Raf-1 kinase-induced down-regulation of a sodium channel was blocked by the MEK inhibitor PD 98059, suggesting that the ERK pathway is involved in the signal transduction (Zentner *et al.*, 1998). The acinar cells respond to nitric oxide (NO), an inflammation-related signaling molecule, by the pathways regulated by ERK and p38 (Slomiany and Slomiany, 2002b). The p38 MAPK pathway is important in transducing stress signals, and p38 MAPK is activated strongly and rapidly by stresses and inflammatory cytokines (Dent *et al.*, 2003). Recently, it was suggested that inhibition of LPS-stimulated iNOS and COX-2 expression and reduced NO release were by a mechanism involving p38 (Brautigam *et al.*, 2005). SS patients show activated forms of p38 and

JNK in infiltrating mononuclear cells (Nakamura et al, 1999). Protein kinases downstream of p38 can activate transcription factors such as activating transcription factor-2 (ATF-2) and growth and DNA damage (GADD)-153 transcription factor. The p38 MAPK family consists of at least 4 isoforms. The specificity of the isoforms activated depends on the cell type, and the nature and strength of the signals (Morin and Huot, 2004). Importantly, the cellular response to p38 MAPK activation is highly cell type dependent: it can induce apoptosis, growth arrest, or differentiation (Slomiany and Slomiany 2002a, Dent *et al.*, 2003, Morin and Huot, 2004). It is known that GTPs modulate the MAPK pathways (Stratton *et al.*, 2000; Singh *et al.*, 2003; Vayalil *et al.*, 2003; Afaq *et al.*, 2003). Importantly, our data indicate that p38 is up-regulated in NHEK and NS-SV-AC cells, targets of SS, by GTPs. Inhibition of GTP-induced p38 activation resulted in disrupted signal transduction in these cells, leading to failure of NHEK differentiation or loss of GTPs protection in NS-SV-AC cells (Hsu *et al.*, 2006).

Conclusions

Autoimmune disorders such as SS and lupus are associated with three major destructive cell-based mechanisms: apoptosis of target cells, autoantigen expression/autoantibody production, and production of pro-inflammatory cytokines. If developed, strategies simultaneously targeting these three systems could provide novel preventive and therapeutic measures to combat autoimmune disorders. Epidemiology evidence suggests that green tea consumption is associated with overall improved health; specifically, in China and Japan, the two leading green tea-consuming countries, the incidence of SS is lower relative to non-green tea consuming countries such as the US. GTPs have been shown to possess the capacity to inhibit apoptosis, suppress autoantigen expression, and down-regulate inflammatory cytokines. Thus, delay of the autoimmune disease onset and/or reduction of the severity of the symptoms might be achieved if GTPs are appropriately administered. Scientific data indicated that GTPs may mediate their effects, at least in part, *via* mechanisms involving the p38 MAPK pathway and antioxidant activity. These observations suggest that characterizing and understanding the effects of GTPs on apoptosis, autoantigen expression and inflammatory cytokine production could facilitate the identification of cellular and molecular mechanisms involved in SS, particularly the role of the p38/MAPK pathway.

Based on the evidence currently available, we hypothesize that: (A) oral administration of GTPs, either via green tea consumption or by other delivery systems, protects the salivary gland from SS-induced tissue destruction by attenuating one or more cell-based mechanisms of pathogenesis (apoptosis, autoantigen gene expression and cytokine production); (B) topical application of GTPs could potentially protect the epidermis from cutaneous manifestation of lupus,

also by attenuating the cell-based mechanisms; and (C) this attenuation is mediated *via* two molecular mechanisms-antioxidant activity and p38 MAPK activation in acinar cells and keratinocytes. However, whether internal organs/tissue could be protected by GTPs from autoimmune disorders is still unknown due to the lack of scientific research. Given the fact that autoimmune diseases affect millions of people, much more and urgent effort is needed to uncover the mechanisms of the diseases and search for alternative remedies. The need to enhance research activities in the United States is evidenced by recent RFA (request for applications) for Sjogren's syndrome research from the National Institute of Health, and the public campaign to increase lupus awareness by popular actresses such as Kellie Martin and Tomiko Fraser. GTPs are likely to be suitable candidates for novel preventive and therapeutic initiatives to manage autoimmune disorders due to their non-toxic and easy to access nature. In addition to GTPs, many other non-toxic phytochemicals also possess antioxidant and/or anti-inflammatory properties, which need to be evaluated for their therapeutic activities against autoimmune disorders.

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